



Evaluation and Outcome of Young Children With Chronic Cough*

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Objective: To evaluate the use of an adult-based algorithmic approach to chronic cough in a cohort of children with a history of > 3 weeks of cough and to describe the etiology of chronic cough in this cohort.

Methods: A prospective cohort study of children referred to a tertiary hospital with a history of > 3 weeks of cough between June 2002 and June 2004. All included children followed a pathway of investigation (including flexible bronchoscopy and evaluation of airway cytology via BAL) until diagnosis was made and/or their cough resolved.

Results: In our cohort of 108 young children (median age 2.6 years), the majority had wet cough (n = 96; 89%), and BAL fluid samples obtained during bronchoscopy led to a diagnosis in 45.4% (n = 49). The most common final diagnosis was protracted bacterial bronchitis (n = 43; 39.8%). These patients had neutrophil levels on BAL samples that were significantly higher than those in other diagnostic groups (p < 0.0001). Asthma, gastroesophageal reflux disease (GERD), and upper airway cough syndrome (UACS), which are common causes of chronic cough in adults, were found in < 10% of the cohort (n = 10).

Conclusions: The adult-based anatomic pathway, which involves the investigation and treatment of patients with asthma, GERD, and UACS first is largely unsuitable for use in the management of chronic cough in young children as the common etiologies of chronic cough in children are different from those in adults. (CHEST 2006; 129:1132-1141)

Key words: airway inflammation; BAL; bronchitis; chronic cough; children; etiology; investigation; management

Abbreviations: CXR = chest radiograph; GER = gastroesophageal reflux; GERD = gastroesophageal reflux disease; HRCT = high-resolution CT; IQR = interquartile range; NR = natural resolution; PBB = protracted bacterial bronchitis; UACS = upper airway cough syndrome

Cough is one of the most common reasons that people consult their doctor.¹ In the pediatric population, it causes significant concern to parents.² Prevalence data have suggested that 35% of pre-school children report cough in any given month.³ A multicentered study of children 7 to 11 years of age found that 9% of these reported chronic cough.⁴

Despite this, there are limited studies defining the causes of this common presenting symptom in the pediatric population, and those that are available show contrasting etiologies.^{5,6} Holinger⁵ and Callahan⁷ both found asthma to be the most common diagnosis in children with chronic cough, while a more recent study by Thomson et al⁶ found that none of the children in their cohort had asthma as the sole etiology of their cough. Furthermore, studies that have included airway cytology⁸⁻¹⁰ have found

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that airway eosinophilia suggestive of asthma or eosinophilic bronchitis are rare in children with chronic cough.

Based on etiologic studies of chronic cough in adults, an algorithmic approach has been shown to be highly successful and to facilitate the diagnosis of

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cough in up to 99% of cases.¹¹ Some other studies,^{12,13} however, were not able to achieve this very high percentage. There are no studies that have used this approach in children, and this is one of the current gaps in the pediatric literature. The 1998 American College of Chest Physicians guidelines¹⁴ advocated that "the approach to managing chronic cough in children is similar to the approach in adults." While this may appear reasonable, there is a significant body of evidence that has also shown that children are different from adults.¹⁵ The comparison of respiratory disease processes that affect the pediatric population and not adults, such as bronchiolitis, and similarly adults but not children, such as COPD, highlight the differences that must be considered in treating pediatric patients. The physiologic maturation process of the cough reflex and other aspects of respiratory physiology (*eg*, respiratory rate) and non-respiratory physiology (*eg*, immune system maturation) are possible explanations for this.^{15,16}

The aims of this study on children who were referred with chronic cough of > 3 weeks duration were (1) to evaluate the use of an adult-based algorithmic approach in the management of children and (2) to describe the etiology of chronic cough in our cohort of children. We hypothesized that the common etiologies of chronic childhood cough are different to chronic cough in adults and therefore that adult-based protocols are unsuitable for children.

MATERIALS AND METHODS

Subjects

Any child (*ie*, age < 18 years) with chronic cough of unknown etiology who was referred to the pediatric respiratory practice at our university hospital between June 2002 and June 2004 was invited to participate. Chronic cough was defined as a cough of > 3 weeks duration.^{11,14} The children attended an initial visit, which included a detailed medical history and physical examination using a standardized data collection sheet. The history included the duration and character of the cough, family history of atopy and asthma, history of dyspnea or wheeze, allergies, sinusitis, and respiratory tract infections, and smoke exposure. The physical examination included complete ear, nose, and throat, respiratory, and cardiovascular examinations looking particularly for clubbing, chest deformity, cardiac abnormality, or

auscultatory abnormality. Exclusion criteria were infants born prematurely (*ie*, < 37 weeks gestation), children with known lung disease or other severe underlying disorders such as gross neurodevelopmental delay or cardiac abnormalities. The recruited control group were children having bronchoscopy (for the assessment of stridor) with no history of chronic cough and no acute respiratory infection in the preceding 4 weeks. Written informed consent was obtained, and the study was approved by the ethics committee of our institution.

Study Protocol

The study protocol used was based on the adult algorithm for chronic cough that was modified for children (Fig 1).^{11,14} The major modification was the evaluation order of diagnostic tests, with bronchoscopy and BAL being performed significantly earlier than in the adult protocol. We chose to perform bronchoscopy in all patients in whom cough had persisted beyond initial investigations to obtain BAL fluid samples for cytology, microbiology, and inflammatory marker evaluation in an attempt to better understand the etiologic conditions associated with chronic cough in children. We also elected to perform relevant childhood investigations, such as the sweat chloride test, at the beginning of the investigative protocol. The children followed the pathway (Fig 1) until a diagnosis was made and/or their cough resolved. If investigations did not lead to a diagnosis, then a trial of medications (based on the results of the history and physical examination) was used for a defined period (2 to 4 weeks). The children were followed-up and cough diary data were recorded until cough resolution, to a maximum of 12 months after study enrollment.¹⁷

Clinical and Laboratory Techniques

Induced Sputum (for Children > 6 Years of Age): The technique involved the incremental inhalation of a 4.5% hypertonic saline solution via an ultrasonic nebulizer, as described previously.¹⁸ The initial sputum sample was utilized for microbiological assessment; the rest of the sample was pooled for total cell count and differential cell count, as described elsewhere.¹⁹

Flexible Bronchoscopy: Flexible bronchoscopy (Olympus; Tokyo, Japan) was performed under general anesthetic, as previously described.²⁰ The BAL fluid sample was obtained according to European Respiratory Society guidelines. A sterile normal saline solution in three aliquots of 1 mL/kg (maximum, 20 mL) was instilled into the most affected area (identified radiologically and/or bronchoscopically) or into the right middle lobe in patients with diffuse disease (or the right lower lobe if unable to wedge in the right middle lobe) and was suctioned into a mucus trap. The first aliquot was used for microbiology examination. The second and third aliquots were pooled for cytology and lipid-laden macrophage index.²¹ The recorded information included the yield from BAL, macroscopic appearances, and anatomic abnormalities.

BAL Measurements: Quantitative aerobic cultures of bacteria were undertaken on BAL using standard sterile loops (10 and 100 μ L) on blood and chocolate agar plates for the detection of aerobic bacteria. Plates were incubated at 35°C for 48 h, and isolates were counted and identified. A positive bacterial culture was defined as the growth of a single bacteria species of $\geq 10^5$ cfu/mL.²² Viral studies were also performed on BAL fluid; direct immunofluorescence antigen was used to detect respiratory syncytial virus, adenovirus, parainfluenza viruses 1, 2, and 3, and influenza A and B. If direct immunofluorescence antigen testing results were negative, polymerase chain reaction tests were undertaken for all of the viruses listed above. A cell count was

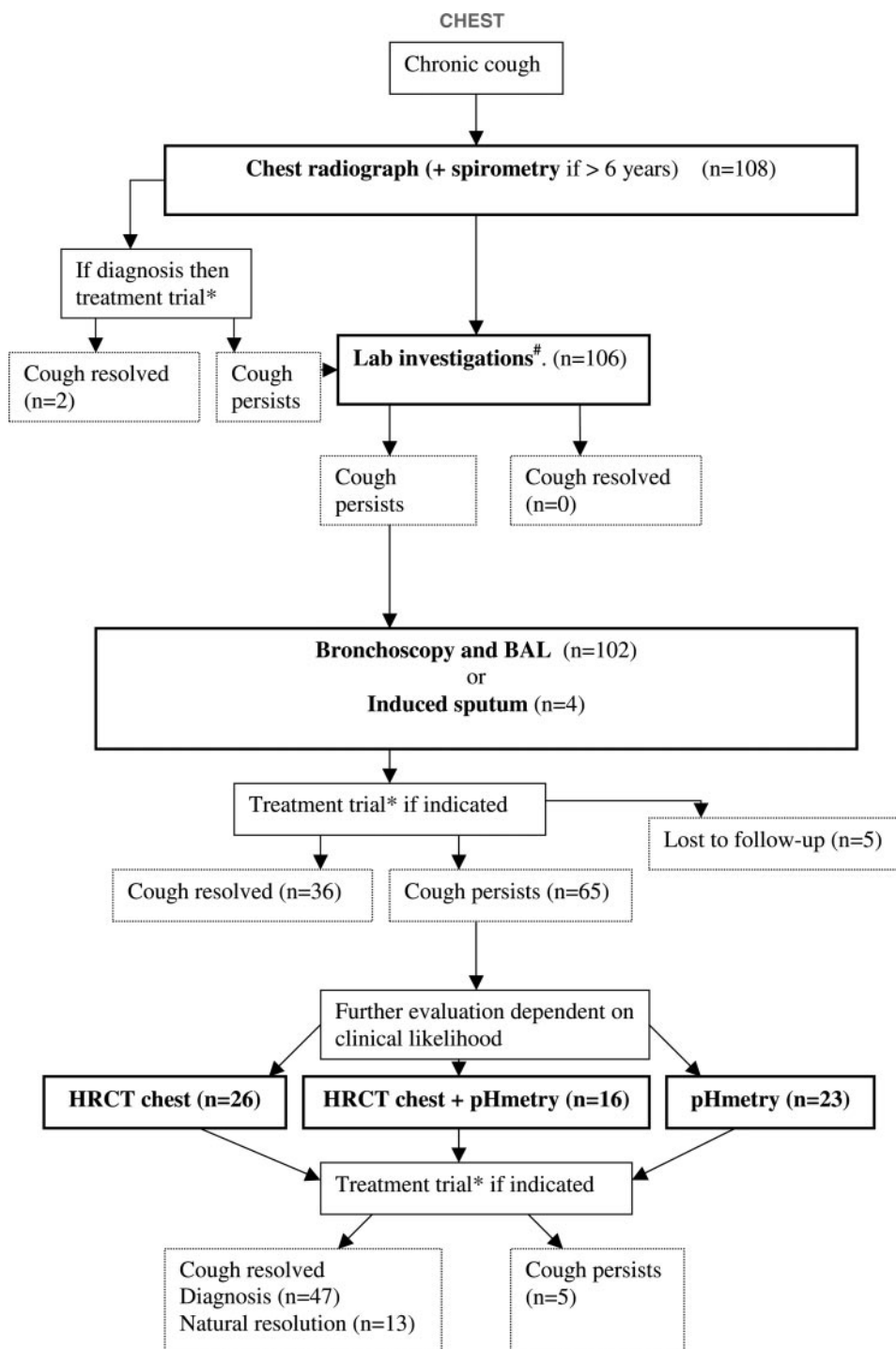


FIGURE 1. Protocol of investigation for children with chronic cough (3 weeks), Royal Children's Hospital, Brisbane, Australia. * = treatment trial for 2-week period; if no improvement, then further evaluation. # = laboratory investigations included sweat chloride test, testing for cystic fibrosis gene mutations (eight most common mutations in Australian population), serum *M pneumoniae* total antibody and *B pertussis* IgA serology, Igs (ie, IgG, IgM, and IgA), and total IgE and IgG subclasses.

performed on the cell suspension, cytocentrifuge slides were prepared and stained (modified Wright stain, DiffQuik; Lab Aids; Narrabeen, NSW, Australia) for cell differential profiles (minimum of 400 cells counted). All cellular examinations were performed by cytologists who were blinded to the children's medical history.

Cough Diary: A cough diary using the verbal category descriptive score for daytime and nocturnal cough was used from study entry until cough resolution. This cough diary has been previously validated as correlating best with an objective measure (cough meter).¹⁷ This involves scoring the cough (as listed below) for each day as follows: 0, no cough; 1, cough for one or two short

periods only; 2, cough for more than two short periods; 3, frequent coughing but does not interfere with school and other activities; 4, frequent coughing that interferes with school and other activities; and 5, cannot perform most activities due to severe coughing. A visual analog scale from 0 to 10 was used for parental rating of cough severity at study enrollment. The cough quality was also documented both by the treating physician and the parents as being either "moist" or "dry."²³ As young children with airway secretions do not expectorate even in the presence of suppurative lung disease, the term *moist cough*, which encompasses productive cough, was utilized.^{24,25} In adults who are able to expectorate, moist cough is usually synonymous with productive cough.

HRCT and pHmetry: The added investigations of high-resolution CT (HRCT) scan of the chest and 24-h ambulatory pHmetry were undertaken if the initial investigations had not led to a diagnosis and the subject was still coughing. They were undertaken as directed by the physician caring for the child, given the semiinvasive nature of these investigations and the potential harmful effects, particularly radiation burden.²⁶ An HRCT scan of the chest was undertaken to clarify or eliminate disorders such as bronchiectasis or interstitial lung diseases.²⁶

Definitions of Diagnostic Categories

Diagnostic categories were reached using standard *a priori* definitions, which included investigation results and response to therapy. Response to therapy was defined as improvement by > 75% according to cough diary data, or the total resolution of the cough.¹⁷ The *a priori* definitions listed were as follows:

1. Definite protracted bacterial bronchitis (PBB): history of chronic moist cough, positive BAL fluid culture, and response to antibiotic treatment (amoxicillin/clavulanic acid suspension, 400 mg/5 mL, at a dosage schedule of 22.5 mg/kg twice daily) with resolution of the cough within 2 weeks.
2. Probable PBB: history of chronic moist cough and either positive BAL culture or immediate response to antibiotic therapy with resolution of the cough within 2 weeks. In most cases of probable PBB, the BAL culture reached only 10³ or 10⁴ cfu/mL or the subjects required a longer duration of antibiotic treatment to achieve cough resolution.
3. Natural resolution (NR): spontaneous resolution of cough without therapy or, if therapies were tried, there was no temporal relationship (2 weeks) to cough resolution.
4. Asthma-like conditions: episodic wheeze and cough with variable airflow limitation demonstrated by bronchodilator responsiveness, and/or response to low-dose inhaled steroids with resolution of cough within the first 2 weeks of treatment.²⁷
5. Bronchiectasis: history of chronic cough and the presence of radiologic bronchiectasis on HRCT scan of the chest.²⁶
6. Primary aspiration: children with recurrent cough with feeds and patchy changes on chest radiograph (CXR).²⁸ The diagnosis was made on the resolution of cough on withdrawing oral fluids combined with supportive investigations including modified barium swallow and HRCT scan changes.
7. Gastroesophageal reflux (GER): reflux index (*ie*, the percentage of time spent with pH < 4) of ≥ 4% on pHmetry or esophageal biopsy sample showing reflux esophagitis, and treatment by standard medical therapy results in resolution of the cough.²⁹
8. Eosinophilic disorders: included eosinophilic bronchitis or hypereosinophilic syndrome. Eosinophilic bronchitis was

defined as an eosinophil count of > 1% of the BAL fluid differential cell count or > 2.5% of the differential cell count in induced sputum samples.²⁷

9. Upper airway cough syndrome (UACS): history consistent with diagnosis and response to specific intranasal therapy within 2 weeks.
10. *Bordetella pertussis* and *Mycoplasma pneumoniae* infections: diagnosis is made if serologic evidence of infection (*B pertussis* IgA positive, rising total antibody titers to *M pneumoniae*) and evidence of these organisms in BAL fluid using polymerase chain reaction.

The remaining diagnoses were all made by standard clinical practice. Diagnoses were made in accordance with the above diagnostic categories, and patients were treated. The primary diagnostic outcome was defined as the diagnosis (and subsequent treatment) that resulted in cough resolution. The secondary diagnoses described are those that were made during the pathway of investigation but for which (1) treatment did not result in the resolution or improvement of the cough or (2) no treatment for this diagnosis was administered and the cough resolved with other treatment or spontaneously.

Statistical Analysis

Children were categorized into diagnostic groups. The patients with definite PBB and probable PBB were statistically analyzed as one group due to their clinical similarities (and are called the *PBB group*). For the statistical analysis of BAL fluid data, the patients will be considered to fall into one of the following three primary diagnostic groups: PBB group; NR group; or "other" diagnostic group (referring to all other diagnostic groups). The χ^2 test was used to compare categorical variables between groups. BAL fluid data were not normally distributed, and thus nonparametric analyses were used (Mann-Whitney test for comparisons between two groups; and Kruskal-Wallis test when more than two groups were compared). Medians and interquartile ranges (IQRs) were used for all descriptive data. A two-tailed p value of < 0.05 was considered to be significant. A statistical software package (SPSS, version 12; SPSS; Chicago, IL) was utilized for all statistical calculations.

RESULTS

The median age of the 108 young children studied (51 male, 57 female) was 2.6 years (IQR, 1.2 to 6.9 years). These children were recruited from 114 who had been invited to participate. The main reason for nonparticipation was an unwillingness to complete the cough diaries and/or further investigations. The prestudy diagnoses were asthma (n = 54; 50%), no preexisting diagnosis (n = 34; 31.5%), and bronchitis (n = 2; 2%), and patients were referred from pediatricians (n = 56; 52%) and general practitioners (n = 44; 41%). The median duration of cough was 6 months (IQR, 3 to 12 months) and 67 patients (62%) experienced the onset of chronic cough within the first year of life. Wet cough was described in 96 patients (89%), and 12 patients (11%) had exclusively dry cough.²³ Exposure to cigarette smoke occurred in 46 households (42.6%). The median verbal category descriptive cough score at study

enrollment was 3.0 (IQR, 2 to 3), and the median visual analog scale was 5.0 (IQR, 3.25 to 7.0).

A flowchart illustrating the pathway to the diagnosis of patients is shown in Figure 1. The investigations undertaken and the abnormalities detected are summarized in Table 1. The obtaining of BAL fluid samples via flexible bronchoscopy was the primary investigation, leading to a diagnosis in 45.4% of the cohort; in a further 6.5%, the results added to the diagnosis. Table 2 shows the percentage of children with abnormal BAL fluid cytology when compared to that in a control group (n = 17) collected during study.

The final primary diagnosis was reached in 98 patients (90.8%); 5 patients (4.6%) were lost to follow-up and 5 patients (4.6%) continued to cough without a diagnosis (Fig 2). The common adult diagnoses of asthma, GER disease (GERD), and chronic upper airways disease were found in 10 patients. A secondary diagnosis was found in 59 patients (55%), as follows: airway malacia disorders (*ie*, tracheomalacia or bronchomalacia), 36 patients (33%); GER, 16 patients (14.8%); and clinical obstructive sleep apnea, 2 patients (1.9%). In a subgroup of children who were > 10 years of age (n = 16), the diagnosis found most commonly was PBB (n = 5; 31%). Other diagnoses in this subgroup included the following: NR, two patients (13%); bronchiectasis, two patients (13%); uncertain, two patients (13%); asthma-like conditions, one patient (6%); *B pertussis* infection, one patient (6%); GERD, one patient (6%); UACS, one patient (6%); and eosinophilic bronchitis, one patient (6%).

The most common primary diagnosis was PBB (n = 43; 39.8%). Definite PBB (n = 24; 22.2%) and probable PBB (n = 19; 17.6%) were clinically similar groups of patients with moist cough and with no statistical differences between characteristics includ-

Table 2—BAL Fluid Cellular Differential Results

Differential Cellular Count	Reference Range*	No. Cases (% Total Cohort)
Neutrophilia†	2.0 (1.0–6.5)	46 (42.6)
Lymphocytosis‡	9.0 (2.5–15.0)	10 (9.3)
Eosinophilia§ ²⁷	0.2 (0.0–0.3)	3 (2.8)
Multiple cell lines increased		4 (3.7)
Normal¶		34 (31.5)

*Reference range is the percentage of all cells in BAL fluid, given as the median (IQR). The reference range obtained via the control group (n = 17) during the study period.

†Defined as > 6.5% neutrophils in BAL fluid.

‡Defined as > 15% lymphocytes in BAL fluid.

§Defined as > 1% eosinophils in BAL fluid.

||Defined as > 1 of the above conditions fulfilled.

¶Defined as none of the above conditions fulfilled.

ing age (p = 0.72), duration of cough (p = 0.10), or neutrophil count in the cellular differential count (p = 0.20). These two groups have therefore been combined to form the PBB diagnostic group. The PBB group BAL fluid median neutrophil percentage (as a percentage of the total number of nucleated cells in BAL fluid) was 40.0%, while the NR median neutrophil percentage was 4.0% (Fig 3). The complete cytologic profile is shown in Table 3. The microbiology of PBB was typical respiratory organisms including *Haemophilus influenzae* (n = 20; 47%), *Moraxella catarrhalis* (n = 11; 26%), and *Streptococcus pneumoniae* (n = 15; 35%). More than one organism grew in significant numbers in a number of patients. All of these organisms were sensitive to treatment with amoxicillin/clavulanic acid. Viral pathogens, including adenovirus (n = 2; 5%) and parainfluenza virus (n = 1; 2%) also grew in three patients within this diagnostic group.

Table 1—Investigations Used and Number With Abnormal Results

Variables	Investigations Performed*	Patients With Abnormalities†	Most Common Abnormalities, No.
CXR	108 (100)	68 (63/63)	Peribronchial thickening, 48; Atelectasis, 11
Spirometry in patients > 6 yr of age	33 (100)	4 (3.7/12.1)	Reversible airways obstruction, 1; mixed restrictive pattern, 3
Bronchoscopy			
Macroscopic appearance	102 (94.4)	92 (85.2/90.2)	Bronchitic changes, 57; malacia disorders, 36
Cellular differential	101 (93.5)	74 (68.5/73.3)	Neutrophilia, 46; Lymphocytosis, 10
Igs and subclasses	105 (97)	7 (6.5/6.7)	IgA deficiency, 3; IgG2 deficiency, 3
CF gene mutations	93 (86)	3 (2.8/3.2)	Single delta F508 gene mutation, 3
Sweat test	71 (66)	0 (0/0)	
IgE	76 (70)	3 (2.8/3.9)	Abnormal IgE level > 2,400 µg/L, 3
HRCT chest	42 (39)	30 (28/71.4)	Bronchiectasis, 6; atelectasis, 4; scarring, 4
pHmetry with or without esophageal biopsy	38 (35)	18 (16.7/47.4)	

*Values are given as No. (%).

†Values are given as No. (% of cohort/% of the No. performed).

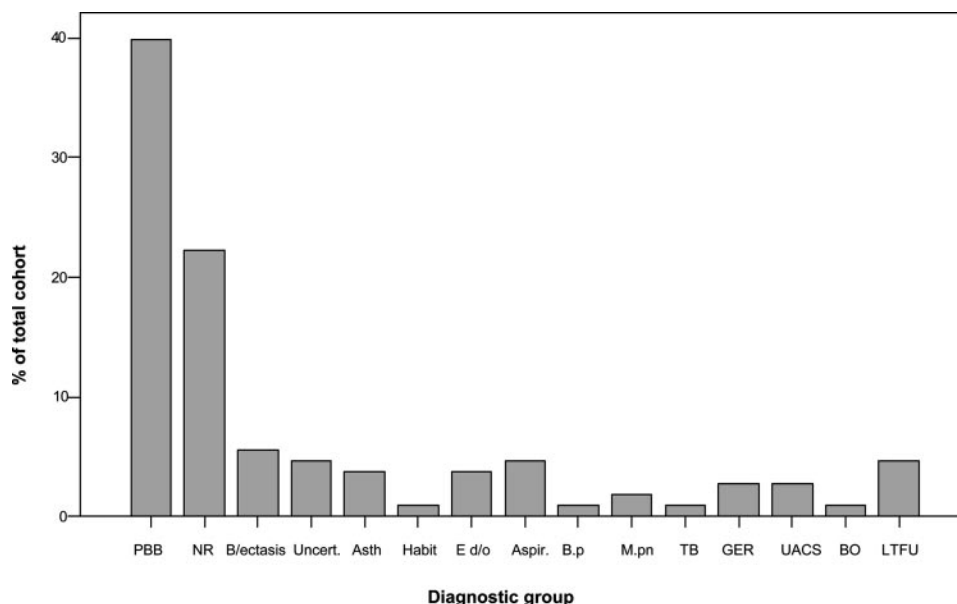


FIGURE 2. Primary diagnoses in children with chronic cough. The spectrum and frequency of primary causes in 108 patients is shown. The most common were PBB in 43 patients (39.8%) and NR in 24 patients (22.2%). Others shown are as follows: bronchiectasis (B/ectasis), six patients; uncertain (Uncert), five patients; asthma-like conditions (Asth), four patients; habit cough (Habit), one patient; eosinophilic disorders (E d/o), four patients; aspiration disorders (Aspir), five patients; *B pertussis* infection (B.p), one patient; *M pneumoniae* infection (M.pn), two patients; endobronchial tuberculosis (TB), one patient; GER, three patients; UACS, three patients; bronchiolitis obliterans (BO), one patient; and lost to follow-up (LTFU), five patients.

DISCUSSION

This is the first study that has prospectively evaluated young children using a modified protocol

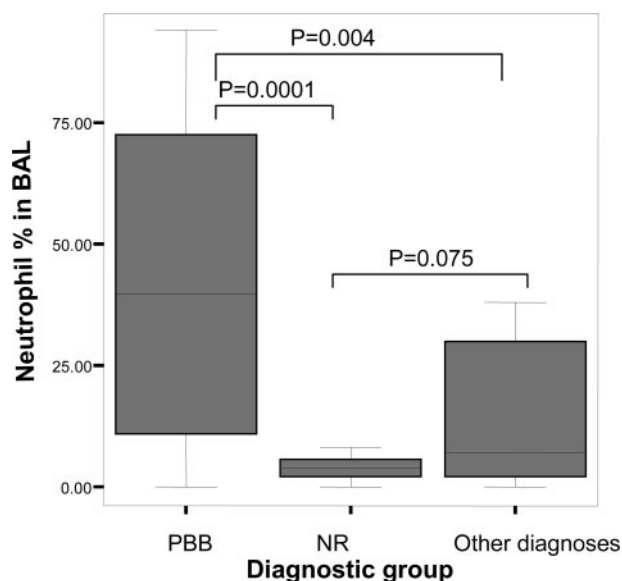


FIGURE 3. Median and IQR of neutrophils in BAL fluid for major diagnostic groups (as a percentage of the total number of nucleated cells).

based on the protocol of Irwin et al¹¹ for chronic cough in adults. We have found that the diagnostic categories for chronic cough in children are heterogeneous and that the most common diagnosis was PBB, with the three most common diagnoses of chronic cough in adults (*ie*, asthma, UACS, or GERD)¹⁴ being found in only 9% of young children.

Adult studies³⁰ have described that a systematic evaluation of cough using an algorithmic approach will lead to diagnosis in > 90% of cases of adult cough and to successful treatment in > 85%. Acknowledging that there was a paucity of data on children, the 1998 American College of Chest Physicians guidelines¹⁴ have recommended that the same diagnostic approach be used to determine the etiology of chronic cough in children and also stated that in nonsmoking adults asthma, UACS, and/or GERD are likely to be the causes of chronic cough in almost all cases. However, using a modified adult investigative protocol we found that the three most common diagnoses of chronic cough in adults were uncommon in young children (< 10%). Instead, we found a heterogeneous group of diagnoses with the two most common diagnoses being PBB and NR. Our findings thus suggest that the highly successful and widely used anatomic pathway of Irwin and colleagues,^{11,14} which involves the investigation and

Table 3—BAL Cellular Count for the Diagnostic Groups PBB and NR*

Cells	PBB Group (n = 38)	NR Group (n = 24)	Other† (n = 35)	p Value‡
Neutrophils, %	40.0 (10.0–73.0)	4.0 (2.0–5.8)	7.0 (2.0–32.5)	< 0.0001
Lymphocytes, %	8.5 (5.0–16.8)	10.0 (6.5–19.8)	8.0 (2.3–12.0)	0.152
Macrophages, %	46 (13–77)	83.0 (62.3–89.8)	80.0 (54–89.5)	< 0.0001
Total cell count, No. × 10 ⁶	350 (233–1,000)	224.0 (121–345)	228.0 (120–330)	0.014

*Values are given as the median (IQR).

†Refers to all diagnoses grouped together excluding the two most common, PBB and NR.

‡Kruskal-Wallis test.

empirical treatment of these three common adult diagnoses initially, should not be applied to young children.

There are few prospective cohort studies in children addressing the causes of chronic cough, and none have used the adult pathway. Published prospective studies^{5,7} in affluent countries have described patients with asthma as being the most common diagnostic group. These cohort studies have failed to define a time frame for the apparent response to treatment; objective tests were rarely used, and cough diaries were not used. In contrast, we defined a temporal response of 2 weeks to cough resolution (in randomized controlled trials of cough therapy resolution has occurred in 2 weeks), which is important in cough studies as the placebo and period effects of cough are large.²⁵ We also utilized validated prospective cough diary cards in our study.¹⁷ Asthma-like conditions were found in only a minority (4%) of children in our cohort. More recent data have shown that children with asthma can certainly present with cough alone, but in most children cough in the absence of wheeze and/or dyspnea is rarely asthma.^{31,32} Although contrasting with the results of previous cohort studies,^{5,7} our findings are in concordance with more recent literature,^{6,33} as well as those that have examined airway cytology.^{8–10,34} Other possible reasons for the differences found in our study in comparison to other prospective studies include era, patient selection, and depth of investigations. In addition to the methodological differences illustrated above, there are obvious discrepancies in the utilization of bronchoscopy as Holinger⁵ used rigid bronchoscopy only and Callahan⁷ performed flexible bronchoscopy in only a small number of his cohort (n = 5).

The most common cause of a secondary diagnosis was lower airway malacia disorders. We have considered a diagnosis to be secondary if discovered during the investigation of the cough but when treated did not result in cough resolution. Thomson and colleagues⁶ described that lower airway malacia disorders were common in a retrospective cohort of

children with chronic cough. The associations between cough and malacia are well-known, but the cause and effect are difficult to prove.^{35–37} GER, a common cause of cough in adults, accounted for only 3% of primary diagnoses and for 15% of secondary diagnoses in our cohort. This confirms the small number of articles in the available pediatric literature, which suggests that GER is infrequently the sole cause of pediatric cough,^{5–7} which is again in contrast to data from the literature on adults.^{11,38} The presence of GER in 15% of our cohort as a secondary diagnosis (*ie*, present but treatment not contributing to cough resolution) supports the assertions of some authors that cough itself can induce GER.^{39,40}

Our protocol deviated from the adult algorithm for chronic cough by Irwin and colleagues^{11,14} in a number of significant ways. The major modification was the evaluation order of diagnostic tests, with bronchoscopy and BAL being performed earlier. It would be impractical to evaluate the adult algorithm without modification in children as there are investigations within it that our pre-school-aged cohort (median age, 2.6 years) could not perform, such as bronchoprovocation challenge testing and the examination of sputum samples for evidence of eosinophilic bronchitis or infection. In young children, the examination of airway profiles is possible only through the use of bronchoscopy and BAL. We also elected to perform relevant childhood investigations, such as the sweat chloride test, at the beginning of the investigative protocol. Finally, our protocol deviates from that of Irwin and colleagues^{11,14} in that he advocates the use of sinus x-rays to investigate UACS. Due to the additional radiation dose and the poor relationship between abnormal sinus x-rays and CT scan findings with symptomatology,^{41,42} we elected to diagnose UACS primarily by means of history and clinical findings, and the subsequent response to treatment. Indeed, although adult studies have found that cough has resolved with the treatment of chronic sinusitis, currently none of the available data have proven that cough can be directly

attributed to sinus disease,⁴³ and that in fact the medications that were used to treat chronic sinusitis perhaps treated the infection of the lower respiratory tract.

For this research project, we utilized a protocol that is not widely applicable, and indeed we are not advocating its general use given the high level of skills necessary, the expense involved, and the possible side effects of the investigations. In clinical practice, a short therapeutic treatment trial may be appropriate in a patient with a suggestive history and examination. Depending on the circumstances, the treating physician may or may not choose to do this after a CXR and spirometry testing. Importantly, if a treatment trial is undertaken, the patient must be reviewed after 2 weeks; if the cough has not resolved or significantly improved, then the treatment should be withdrawn and further investigations should proceed to establish the cause of the cough.

In this study, bronchoscopy was utilized to obtain BAL fluid for cellular and microbiological evaluation and to assess large airway anatomy. The safety and value of bronchoscopy as a tool in pediatric respiratory research has been established in centers with expertise in this field, such as ours.⁴⁴ We have defined the normal range for BAL fluid from a control group that was similar to the ones in the available literature for normal differential cell counts from BAL fluid.^{21,45} However, as we had very low levels of eosinophils in our control group we have used the reference ranges quoted by Gibson et al²⁷ for eosinophils. The use of BAL was particularly helpful in our understanding of the pathology of PBB, whereby higher total cell counts and neutrophilic inflammation were present. Fitch and colleagues⁹ also described increased numbers of neutrophils in BAL fluid from patients in their cohort who had chronic cough and speculated that it may be related to a persistent underlying airways infection. Our results support the speculation by Fitch and colleagues.⁹

The limitations of our current study include the inability to undertake every investigation on the entire cohort due to safety and ethical issues. HRCT chest scans were not performed on all children due to the effects of radiation exposure and repeated general anesthetic associated with this procedure.²⁶ Ambulatory 24-h pHmetry is semiinvasive in children and requires a significant commitment from caregivers, particularly in children of a young age such as those in our cohort. Therefore, these two procedures were performed only in patients in whom the diagnosis was suspected or no diagnosis had been reached, and they continued to cough. Also, the design limitations of a cohort study must also be accepted when reaching our conclusions based on

assigned diagnostic categories. Ideally a randomized controlled trial is necessary for assigning treatment effect. Because recruitment for this study was from tertiary subspecialty clinics, it is possible that the results are not widely generalizable. However, > 50% of our referrals came directly from a community setting, we have recruited children from an early stage of coughing illness (> 3 weeks), and almost all children referred to our center were enrolled in the study. These factors minimize selection bias, and one would expect the results to be widely applicable. In addition, the majority of the studies that evaluated the adult protocol were performed in a single tertiary subspecialty clinic,^{11,46} and the results have subsequently been shown to be generalizable to other adult settings.^{47,48}

We recruited all children with chronic cough who were < 18 years of age and had been referred to our department; the vast majority were pre-school-aged children. This is representative of the typical pediatric chronic cough population in Australia. Only a small percentage of children in our study were aged > 10 years (15%); therefore, this study cannot comment specifically on this subgroup of patients. Beyond 14 years of age, the original adult protocol of Irwin and colleagues^{11,13} may be more suitable, but further research into the optimal management of cough in adolescents is needed.

This prospective cohort study has defined the causes of chronic cough in a pediatric population who had been referred to a tertiary outpatient clinic. The use of an investigative pathway established the cause of cough in 90% of patients. We found that PBB was the most common cause of the 14 different diagnoses in this group. Unlike chronic cough studies in adults, asthma, GERD, and UACS were uncommon, indicating that the adult anatomic pathway,^{11,14} which involves the investigation and treatment of these three conditions first, is not directly applicable to young children. We conclude that the etiology of chronic cough in children is different in adults, and that the adult-based algorithmic pathway is largely unsuitable for the management and treatment of young children. Ongoing research to further describe the clinical picture of PBB in children is required.

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